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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,077	06/30/2003	Paul D'Angio	9516-034-999	7850

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EXAMINER	
ROBERTS, LEZAH	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,077	D'ANGIO ET AL.	
	Examiner	Art Unit	
	Lezah W. Roberts	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 24-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 24-35 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Specification

The disclosure is objected to because of the following informalities: on page 5 of the specification, applicant uses # 0 for capsule size when disclosing the 50 mg capsule invention. It is believed this should read # 4 capsule.

Appropriate correction is required.

Claims

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Andrulis *et al.* and Gennaro.

Claim 24 is drawn to single unit dosage forms comprising of 50 mg of thalidomide and 74 mg of a carrier in a size 4 capsule, where the thalidomide makes up about 40 weight percent of the composition.

Andrulis, Jr. *et al.* (5,643,915) disclose several different thalidomide oral unit dosage compositions containing 40 weight percent of thalidomide and 60 weight percent of carrier (column 13, examples 6 and 7). These unit dosage compositions included one 60 mg thalidomide containing composition in tablet form and one with 80 mg of thalidomide in capsule form. The percent weight of the active ingredient thalidomide ranged from 5 or 10 to about 70 weight percent (column 11, lines 53-55). Andrulis, Jr. *et al.* also discloses use of different carriers for the thalidomide compositions, in which he refers to as carders, such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like (column 11, lines 55-59). It was also stated if the active ingredient was encapsulated, the capsule itself could act as the carrier. Magnesium stearate was used in Andrulis, Jr. *et al.'s* compositions ranging from 0.5 to 22 mg, 0.3 to 4.4 weight percent. Some of the binders used in their reported compositions were starch and microcrystalline cellulose. The pharmaceutical preparation was preferably in unit dosage form. Different types of solid dosage forms disclosed included tablets, lozenges, cachet, or capsules. Thalidomide was indicated as combinable with other drugs within a capsule and q.s. the combination with a carrier to the selected capsule size (column 12, line 66). Although not, stated the exact capsule size is dependent on the amount of

composition possessed. Andrulis Jr. *et al.* does not teach the compositions having exactly 50 or 100 mg amounts of thalidomide, the reference nevertheless teaches compositions with different amounts of active ingredient. Within this report, the dosage amount of thalidomide that would have a therapeutic effect was summarized. The amounts ranged from 30 mg to 1500 mg preferably 200 mg to 500 mg, which brackets the amounts recited in the current claims (column 10, lines 43-48).

Gennaro teaches methods of formulating and making pharmaceutical compositions. There is a preference for capsules over that of tablets because they are tasteless, easily administered and easily filled with the drug composition. There is also a consumer preference for capsules (page 1642, paragraph 2). Capsule sizes range from 000 to 5, largest to smallest. Their capsule fill weight ranges from 600 to 30 mg respectively. Each size capsule holds an amount dependent on the powder density. For example a size four capsule is indicated as holding up to 168 mg of a powder with a 0.8 powder density. A size two capsule could hold up to 296 mg and a size zero capsule could hold up to 544 mg (page 1644, Table 5, see also Table 1 within). Gennaro also mentions different types of lubricants and binders commonly used in pharmaceutical compositions. It is important to use lubricants for facile filling of the capsules and to stabilize the drug against moisture. Lubricants commonly used are magnesium stearate, talc, calcium stearate and stearic acid. They are used in concentrations lower than 1% of the total composition. Binders are also used in pharmaceutical compositions. Some include starch, gelatin, sugars, and methylcellulose. The binders make up the rest of the composition and are dependent on the percentage of active ingredient.

Table 1

Capsule Size (0.8)	Capsule Volume (mg)
4	168
3	240
2	296
1	400
0	544

As of the filing date of this application, 50 mg capsules were available in the US with a capsule size of 0 comprising of 50 mg of thalidomide and about 350 mg of carrier. Based on the combined references, it would have been obvious and motivated one of ordinary skill in the art to make smaller capsules by decreasing the amount of carrier and to decrease the capsule size in order to make swallowing multiple capsules easier on the patient increasing patient compliance. It would also be obvious to use pharmaceutical composition ratios already established. The range of active compound reported by Andrulis, Jr. *et al.* was 10 to about 70 weight percent of active compound. When using a size two capsule and assuming 168 mg weight capacity, the range for the amount of drug within the capsule would be 16.8 to 117.6 mg of the thalidomide. This encompasses the amount of thalidomide, 50 mg, included in the present invention. The claimed invention also includes thalidomide in 40 weight percent of the composition also indicated within the specification as the preferable weight percent. This not only falls within the range of the percentages disclosed by Andrulis, Jr. *et al*, but also corresponds with the ratios of thalidomide to carrier used by Andrulis, Jr. *et al.* The invention of claim 24 is obvious to one of ordinary skill in the art absent factual evidence to the contrary.

Claims 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrulis, Jr. *et al* and Gennaro as applied to claim 24 above, and further in view of Govindarajan *et al.*

Claim 25-28 teaches a single unit dosage form of thalidomide comprising or about 50 mg of thalidomide, about 74 mg of carrier which is pre-gelatinized corn starch, and about 1 mg magnesium stearate to make a composition weighing about 125 mg in a size 4 capsule (40 : 59.2 : 0.8, ratio).

Andrulis, Jr. *et al.* discloses thalidomide compositions that overlap that which is being claimed. Andrulis disclose a composition comprising 60 mg of thalidomide, 45 mg starch and 0.5 mg magnesium stearate.

Gennaro lists cornstarch as a widely used carrier or binder for the making of oral single dosage forms (page 1618, first column).

Govindarajan *et al.* discloses several binders for the use of pharmaceutical compositions one of which is pre-gelatinized starch and said binders being present from about 50 to 99 weight percent (US 6,914,067, column 10 and 11)

It would be obvious to one of ordinary skill to use these references in combination to make a 100 mg capsule containing thalidomide. Applicant uses the word "about 50 mg" therefore encompassing 60 mg of thalidomide. When looking for the definition of about in the specification, applicant discloses a range stating, "Preferably, the amount of active ingredient is from about 30 to 50 weight percent, more preferably about 40 weight percent when the active ingredient is about 25 mgs or more". This definition places Andrulis, Jr. *et al.*'s composition within the definition found with in the

applicant's specification. The starch falls into the same chemical family as the pre-gelatinized cornstarch used within the claimed invention as disclosed by the applicant when they disclosed the suitable carriers for their inventions i.e. "sorbitol, starch (e.g., pregelatinized)". In regards to using magnesium stearate, about 1 mg is about 0.8 weight percent placing it in the range of the prior art's weight percent of 0.3 – 4.4 and also encompasses normal protocol for adding a lubricant. It would be obvious to one of ordinary skill to use about 1 mg of magnesium stearate in a drug composition because it is a common and extremely effective lubricant. On the market at the time of the filing date, a 50 mg capsule was available from Celgene in a size zero capsule. It would be obvious to scale down the size of the capsule by reducing the inactive ingredients. In the case of the applicant, the carrier makes up 60 weight percent. This is in the range of universally accepted carrier amount percentages. The invention of claim 25-28 is obvious to one of ordinary skill in the art absent factual evidence to the contrary.

Claims 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrulis, Jr. *et al* and Gennaro as applied to claims 24-28 above, and further in view of Baker *et al.* and Teo *et al.*

Claim 29-30 teaches a single unit dosage of 100 mg of thalidomide and 250 mg of carrier, including magnesium stearate, in a size 2 capsule.

Baker et al. discloses the use of thalidomide in 100 mg capsules also known as Sauramide manufactured by Penn Pharmaceuticals, UK (see abstract).

Teo *et al.* disclosed the use of a 100 mg capsule obtained from Cia Zeetechnica Agraria of Sao Paulo Brazil (1999, page 1163, column 2). There are 100 mg tablets

available under the name Talizer® (2000, page 34, column 2, material). These references do not teach the pharmaceutical formulations.

One of ordinary skill in the art would have found it and been motivated to make 100 mg capsules to accommodate patients who must take high dosages of thalidomide. It would cut down on the number of capsules the patient must imbibe from what was readily available in the US (50 mg). It is also obvious because 100 mg capsules already exist and it would be obvious to adjust the amount of carrier and capsule size to fit one's purposes. The percent composition of the 100 mg dosage form of thalidomide including the magnesium stearate is also encompassed within the prior art as stated above. The size 2 capsules can hold up to 260 mg and it would be obvious to use this size capsule for a 40 weight percent dosage form of a 100 mg thalidomide composition. The thalidomide amount claimed by applicant would only take up 38.5 weight percent of the capsule leaving 61.5 percent for the carrier. This percentage is encompassed within the prior art. Thalidomide tablets existed in 100 mg dosage forms and it would be obvious to one of ordinary skill in the art to make a capsule in order to provide a tasteless dosage form and also accommodate patients who prefer capsules over tablets. This is clearly seen in the market today for example, aspirin and sinus medicines. The invention of claim 29 is obvious to one of ordinary skill in the art absent factual evidence to the contrary.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Andrulis, Jr. *et al.* and Gennaro as applied to claim 24 above, and further in view of Scheffler et al.

Claim 31 teaches a single unit dosage form of about 200 mg of thalidomide and 297.5 mg of a carrier in the form of a size 0 capsule.

Andrulis, Jr. *et al.* used for an example "a gelatin capsule containing 200 mg of thalidomide" (column 10, line 30-31) along with what was mentioned above.

Scheffler *et al.* teaches a 200 mg/day oral dosage is well tolerated (page 489, column 1, last paragraph).

The references combined would motivate someone of ordinary skill in the art to make single dosage form containing 200 mg. There is clearly a need for those requiring dosages of 200 mg or more of thalidomide and to distribute the predetermined dosage form in a convenient package. In regards to the references it would be obvious to one of ordinary skill in the art of how to make a 200 mg thalidomide capsule. Based on the prior art, when using a size zero capsule and assuming 544 mg weight capacity, the range for the amount of drug within the capsule would be 54.4 to 380.8 mg of the thalidomide according to Andrulis, Jr. *et.al.* This range encompasses the amount of thalidomide, 200 mg, included in the present invention. It would also be obvious to one of ordinary skill in the art making a 40 weight percent composition to use a size 0 capsule. The invention of claim 31 is obvious to one of ordinary skill in the art absent factual evidence to the contrary.

Claims 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrulis, Jr. *et al.*, Gennaro, and Govindarajan *et al.* as applied to claims 25-28 above, further in view of and Scheffler *et al.*

Claims 31-35 teach a single dosage unit containing about 200 mg of thalidomide, about 297.5 mg of carrier and about 2.5 mg of magnesium stearate for a total of about 500 mg in a size zero capsule.

It would be obvious to one of ordinary skill in the art to combine these references to make a 200 mg capsule (see above). It would also be obvious to one of ordinary skill in the art making a 200 mg thalidomide capsule with a 40 weight percent of thalidomide to use a size zero capsule. The thalidomide would encompass 36.8 weight percent of the capacity of the capsule. This would leave enough space for the pre-gelatinized cornstarch and magnesium stearate in which would only encompass about 55.1 weight percent capacity. It would be obvious to scale a known percent composition to one's own purposes. The invention of claim 31-35 is obvious to one of ordinary skill in the art absent factual evidence to the contrary.

Claims 24-35 are rejected.

No claims are allowed.

Thalidomide was widely known to have been marketed as Gruenenthal in 100 mg tablets in Germany in the 50s and 60s.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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